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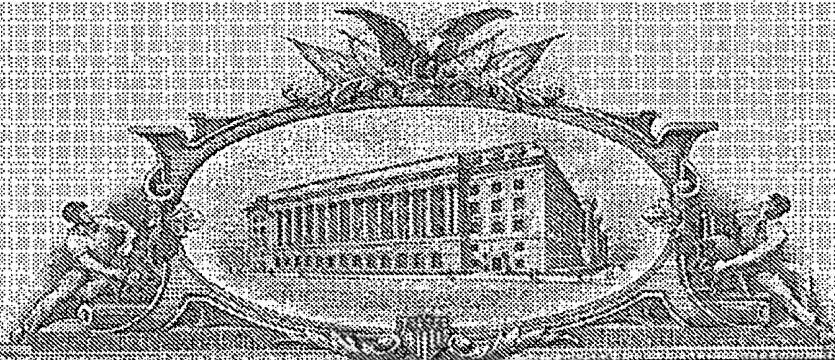
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## PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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<input checked="" type="checkbox"/> Additional inventors are being named on the 1 separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
MPTENS AS MODIFIERS OF THE PTEN/IGF PATHWAY AND METHODS OF USE					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
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[Page 1 of 2]

Respectfully submitted,

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Date

5/14/03

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REGISTRATION NO.

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Docket Number:

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**PROVISIONAL APPLICATION COVER SHEET**  
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Docket Number		EX03-029P
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[Page 2 of 2]

Number 1 of 1

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EX03-029P

## MPTENS AS MODIFIERS OF THE PTEN/IGF PATHWAY AND METHODS OF USE

### BACKGROUND OF THE INVENTION

Somatic mutations in the PTEN (Phosphatase and Tensin homolog deleted on chromosome 10) gene are known to cause tumors in a variety of human tissues. In addition, germline mutations in PTEN are the cause of human diseases (Cowden disease and Bannayan-Zonana syndrome) associated with increased risk of breast and thyroid cancer (Nelen MR et al. (1997) *Hum Mol Genet*, 8:1383-1387; Liaw D et al. (1997) *Nat Genet*, 1:64-67; Marsh DJ et al. (1998) *Hum Mol Genet*, 3:507-515). PTEN is thought to act as a tumor suppressor by regulating several signaling pathways through the second messenger phosphatidylinositol 3,4,5 triphosphate (PIP3). PTEN dephosphorylates the D3 position of PIP3 and downregulates signaling events dependent on PIP3 levels (Maehama T and Dixon JE (1998) *J Biol Chem*, 273:13375-8). In particular, pro-survival pathways downstream of the insulin-like growth factor (IGF) pathway are regulated by PTEN activity. Stimulation of the IGF pathway, or loss of PTEN function, elevates PIP3 levels and activates pro-survival pathways associated with tumorigenesis (Stambolic V et al. (1998) *Cell*, 95:29-39). Consistent with this model, elevated levels of insulin-like growth factors I and II correlate with increased risk of cancer (Yu H et al (1999) *J Natl Cancer Inst* 91:151-156) and poor prognosis (Takanami I et al, 1996, *J Surg Oncol* 61(3):205-8).

PTEN sequence is conserved in evolution, and exists in mouse (Hansen GM and Justice MJ (1998) *Mamm Genome*, 9(1):88-90), *Drosophila* (Goberdhan DC et al (1999) *Genes and Dev*, 24:3244-58; Huang H et al (1999) *Development* 23:5365-72), and *C. elegans* (Ogg S and Ruvkun G, (1998) *Mol Cell*, (6):887-93). Studies in these model organisms have helped to elucidate the role of PTEN in processes relevant to tumorigenesis. In *Drosophila*, the PTEN homolog (dPTEN) has been shown to regulate cell size, survival, and proliferation (Huang et al, *supra*; Goberdhan et al, *supra*; Gao X et al, 2000, 221:404-418). In mice, loss of PTEN function increases cancer susceptibility (Di Cristofano A et al (1998) *Nature Genetics*, 19:348-355; Suzuki A et al (1998) *Curr. Biol.*, 8:1169-78).

EX03-029P

In addition, a member of the IGF/insulin receptor family exists in *Drosophila* and has been shown to respond to insulin stimulation (Fernandez-Almonacid R, and Rozen OM (1987) *Mol Cell Bio*, (8):2718-27). Similar to PTEN, studies in *Drosophila* (Brogiolo W et al (2001) *Curr Biol*, 11(4):213-21) and mouse (Moorehead RA et al (2003) *Oncogene*, 22(6):853-857) establish a conserved role for the IGF/insulin pathway in growth control.

The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Mechler BM et al., 1985 *EMBO J* 4:1551-1557; Gateff E. 1982 *Adv. Cancer Res.* 37: 33-74; Watson KL., et al., 1994 *J Cell Sci.* 18: 19-33; Miklos GL, and Rubin GM. 1996 *Cell* 86:521-529; Wassarman DA, et al., 1995 *Curr Opin Gen Dev* 5: 44-50; and Booth DR. 1999 *Cancer Metastasis Rev.* 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism or cell having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype, such as altered cell growth. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When inactivation of either gene is not lethal, but inactivation of both genes results in reduced viability or death of the cell, tissue, or organism, the interaction is defined as "synthetic lethal" (Bender, A and Pringle J, (1991) *Mol Cell Biol*, 11:1295-1305; Hartman J et al, (2001) *Science* 291:1001-1004; US PAT No:6,489,127). In a synthetic lethal interaction, the modifier may also be identified as an "interactor". When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as

EX03-029P

the IGF pathway, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

### SUMMARY OF THE INVENTION

We have discovered genes that modify the PTEN/IGF pathway in *Drosophila* cells, and identified their human orthologs, hereinafter referred to as modifier of PTEN/IGF (MPTEN). The invention provides methods for utilizing these PTEN/IGF modifier genes and polypeptides to identify MPTEN-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired PTEN/IGF function and/or MPTEN function. Preferred MPTEN-modulating agents specifically bind to MPTEN polypeptides and restore PTEN/IGF function. Other preferred MPTEN-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MPTEN gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MPTEN modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MPTEN polypeptide or nucleic acid. In one embodiment, candidate MPTEN modulating agents are tested with an assay system comprising a MPTEN polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate PTEN/IGF modulating agents. The assay system may be cell-based or cell-free. MPTEN-modulating agents include MPTEN related proteins (e.g. dominant negative mutants, and biotherapeutics); MPTEN -specific antibodies; MPTEN -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MPTEN or compete with MPTEN binding partner (e.g. by binding to an MPTEN binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In specific

EX03-029P

embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate PTEN/IGF pathway modulating agents are further tested using a second assay system that detects changes in the PTEN/IGF pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the PTEN/IGF pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MPTEN function and/or the PTEN/IGF pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MPTEN polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated the PTEN/IGF pathway.

#### DETAILED DESCRIPTION OF THE INVENTION

The PTEN co-RNAi plus insulin synthetic lethal screen was designed to identify modifier genes that are lethal or reduce proliferation in cells with a hyperstimulated IGF/insulin pathway, but not in normal cells. We created cells with a hyperstimulated IGF/insulin pathway by treatment with insulin and RNAi-mediated inactivation of dPTEN, the Drosophila homologue of the human tumor suppressor PTEN. In addition to identifying genes with synthetic lethal interactions in insulin-treated, PTEN-deficient cells, this screen identified genes that, when inactivated, preferentially reduced the viability of insulin-treated, PTEN-deficient cells relative to normal cells. Modifier genes haing a synthetic interaction with the PTEN/IGF pathway were identified. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MPTEN genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective IGF signaling pathway, such as cancer. Table 1 lists the modifiers and their orthologs.

EX03-029P

In vitro and in vivo methods of assessing MPTEN function are provided herein. Modulation of the MPTEN or their respective binding partners is useful for understanding the association of the PTEN/IGF pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for PTEN/IGF related pathologies. MPTEN-modulating agents that act by inhibiting or enhancing MPTEN expression, directly or indirectly, for example, by affecting an MPTEN function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MPTEN modulating agents are useful in diagnosis, therapy and pharmaceutical development.

#### **Nucleic acids and polypeptides of the invention**

Sequences related to MPTEN nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the appended sequence listing.

The term "MPTEN polypeptide" refers to a full-length MPTEN protein or a functionally active fragment or derivative thereof. A "functionally active" MPTEN fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MPTEN protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MPTEN proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MPTEN polypeptide is a MPTEN derivative capable of rescuing defective endogenous MPTEN activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an MPTEN, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MPTEN polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising

EX03-029P

at least 25 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of an MPTEN. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MPTEN nucleic acid" refers to a DNA or RNA molecule that encodes a MPTEN polypeptide. Preferably, the MPTEN polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MPTEN. Methods of identifying orthologs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD *et al.*, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the

EX03-029P

sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, *Advances in Applied Mathematics* 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, *Genomics* 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: *Atlas of Protein Sequences and Structure*, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 *Nucl. Acids*



EX03-029P

Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of an MPTEN. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, Current Protocol in Molecular Biology, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule of an MPTEN under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 µg/ml herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 µg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 µg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20

EX03-029P

$\mu$ g/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

**Isolation, Production, Expression, and Mis-expression of MPTEN Nucleic Acids and Polypeptides**

MPTEN nucleic acids and polypeptides, are useful for identifying and testing agents that modulate MPTEN function and for other applications related to the involvement of MPTEN in the PTEN/IGF pathway. MPTEN nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MPTEN protein for assays used to assess MPTEN function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (*e.g.*, Higgins SJ and Hames BD (eds.) *Protein Expression: A Practical Approach*, Oxford University Press Inc., New York 1999; Stanbury PF et al., *Principles of Fermentation Technology*, 2<sup>nd</sup> edition, Elsevier Science, New York, 1995; Doonan S (ed.) *Protein Purification Protocols*, Humana Press, New Jersey, 1996; Coligan JE et al, *Current Protocols in Protein Science* (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MPTEN is expressed in a cell line known to have defective PTEN/IGF function. The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

EX03-029P

The nucleotide sequence encoding an MPTEN polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MPTEN gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MPTEN gene product, the expression vector can comprise a promoter operably linked to an MPTEN gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MPTEN gene product based on the physical or functional properties of the MPTEN protein in *in vitro* assay systems (*e.g.* immunoassays).

The MPTEN protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (*i.e.* it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MPTEN gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MPTEN proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate

EX03-029P

methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MPTEN or other genes associated with the PTEN/IGF pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (e.g. by gene knock-out or blocking expression that would otherwise normally occur).

#### **Genetically modified animals**

Animal models that have been genetically modified to alter MPTEN expression may be used in *in vivo* assays to test for activity of a candidate PTEN/IGF modulating agent, or to further assess the role of MPTEN in a PTEN/IGF pathway process such as apoptosis or cell proliferation. Preferably, the altered MPTEN expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MPTEN expression. The genetically modified animal may additionally have altered PTEN/IGF expression (e.g. PTEN/IGF knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, i.e. mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (i.e., in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see

EX03-029P

U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, *Science* (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) *Nature* 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, *Methods Mol Biol.* (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, *Experientia* (1991) 47:897-905; for transgenic rats see Hammer *et al.*, *Cell* (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) *Nature* 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MPTEN gene that results in a decrease of MPTEN function, preferably such that MPTEN expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MPTEN gene is used to construct a homologous recombination vector suitable for altering an endogenous MPTEN gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, *Science* (1989) 244:1288-1292; Joyner *et al.*, *Nature* (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, *Science* (1989) 244:1281-1288; Simms *et al.*, *Bio/Technology* (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific

EX03-029P

gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH et al., (1994) Scan J Immunol 40:257-264; Declerck PJ et al., (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MPTEN gene, e.g., by introduction of additional copies of MPTEN, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MPTEN gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al. (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X et al (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the PTEN/IGF pathway, as animal models of disease and disorders implicating defective PTEN/IGF function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MPTEN function and phenotypic changes are compared with appropriate control animals such as genetically

EX03-029P

modified animals that receive placebo treatment, and/or animals with unaltered MPTEN expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MPTEN function, animal models having defective PTEN/IGF function (and otherwise normal MPTEN function), can be used in the methods of the present invention. For example, a mouse with defective PTEN function can be used to assess, *in vivo*, the activity of a candidate PTEN modulating agent identified in one of the *in vitro* assays described below. Transgenic mice with defective PTEN function have been described in literature (Di Cristofano et al, *supra*). Preferably, the candidate PTEN/IGF modulating agent when administered to a model system with cells defective in PTEN/IGF function, produces a detectable phenotypic change in the model system indicating that the PTEN/IGF function is restored, i.e., the cells exhibit normal cell cycle progression.

#### **Modulating Agents**

The invention provides methods to identify agents that interact with and/or modulate the function of MPTEN and/or the PTEN/IGF pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the PTEN/IGF pathway, as well as in further analysis of the MPTEN protein and its contribution to the PTEN/IGF pathway. Accordingly, the invention also provides methods for modulating the PTEN/IGF pathway comprising the step of specifically modulating MPTEN activity by administering a MPTEN-interacting or -modulating agent.

As used herein, an "MPTEN-modulating agent" is any agent that modulates MPTEN function, for example, an agent that interacts with MPTEN to inhibit or enhance MPTEN activity or otherwise affect normal MPTEN function. MPTEN function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MPTEN - modulating agent specifically modulates the function of the MPTEN. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MPTEN polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MPTEN. These phrases also encompass



EX03-029P

modulating agents that alter the interaction of the MPTEN with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MPTEN, or to a protein/binding partner complex, and altering MPTEN function). In a further preferred embodiment, the MPTEN- modulating agent is a modulator of the PTEN/IGF pathway (e.g. it restores and/or upregulates PTEN/IGF function) and thus is also a PTEN/IGF- modulating agent.

Preferred MPTEN-modulating agents include small molecule compounds; MPTEN- interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19<sup>th</sup> edition.

#### **Small molecule modulators**

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight less than 10,000, preferably less than 5,000, more preferably less than 1,000, and most preferably less than 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MPTEN protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products, particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MPTEN-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

EX03-029P

Small molecule modulators identified from screening assays, as described below, can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the PTEN/IGF pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

#### Protein Modulators

Specific MPTEN-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the PTEN/IGF pathway and related disorders, as well as in validation assays for other MPTEN-modulating agents. In a preferred embodiment, MPTEN-interacting proteins affect normal MPTEN function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MPTEN-interacting proteins are useful in detecting and providing information about the function of MPTEN proteins, as is relevant to PTEN/IGF related disorders, such as cancer (e.g., for diagnostic means).

An MPTEN-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MPTEN, such as a member of the MPTEN pathway that modulates MPTEN expression, localization, and/or activity. MPTEN-modulators include dominant negative forms of MPTEN-interacting proteins and of MPTEN proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MPTEN-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g.,

EX03-029P

Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3<sup>rd</sup>, Trends Genet (2000) 16:5-8).

An MPTEN-interacting protein may be an exogenous protein, such as an MPTEN-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MPTEN antibodies are further discussed below.

In preferred embodiments, an MPTEN-interacting protein specifically binds an MPTEN protein. In alternative preferred embodiments, an MPTEN-modulating agent binds an MPTEN substrate, binding partner, or cofactor.

### ***Antibodies***

In another embodiment, the protein modulator is an MPTEN specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MPTEN modulators. The antibodies can also be used in dissecting the portions of the MPTEN pathway responsible for various cellular responses and in the general processing and maturation of the MPTEN.

Antibodies that specifically bind MPTEN polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MPTEN polypeptide, and more preferably, to human MPTEN. Antibodies may be polyclonal, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')<sub>2</sub> fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MPTEN which are particularly antigenic can be selected, for example, by routine screening of MPTEN polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MPTEN. Monoclonal antibodies with affinities of  $10^8 \text{ M}^{-1}$  preferably  $10^9 \text{ M}^{-1}$  to  $10^{10} \text{ M}^{-1}$ , or stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press,

EX03-029P

New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MPTEN or substantially purified fragments thereof. If MPTEN fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of an MPTEN protein. In a particular embodiment, MPTEN-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MPTEN-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MPTEN polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MPTEN polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

EX03-029P

MPTEN-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose

EX03-029P

solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml.

Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

#### *Specific biotherapeutics*

In a preferred embodiment, an MPTEN-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MPTEN is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MPTEN, as described in the previous section, may be used as biotherapeutic agents.

When the MPTEN is a receptor, its ligand(s), antibodies to the ligand(s) or the MPTEN itself may be used as biotherapeutics to modulate the activity of MPTEN in the PTEN/IGF pathway.

#### **Nucleic Acid Modulators**

Other preferred MPTEN-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MPTEN activity. Preferred nucleic acid modulators interfere with the function of the MPTEN nucleic acid such as DNA replication, transcription, translocation of the MPTEN RNA to the site of protein translation, translation of protein from the MPTEN RNA, splicing of

EX03-029P

the MPTEN RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MPTEN RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MPTEN mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MPTEN-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphoramidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MPTEN nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem.



EX03-029P

Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al., Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MPTEN-specific nucleic acid modulator is used in an assay to further elucidate the role of the MPTEN in the PTEN/IGF pathway, and/or its relationship to other members of the pathway. In another aspect of the invention, an MPTEN-specific antisense oligomer is used as a therapeutic agent for treatment of PTEN/IGF-related disease states.

#### Assay Systems

The invention provides assay systems and screening methods for identifying specific modulators of MPTEN activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MPTEN nucleic acid or protein. In general, secondary assays further assess the activity of a MPTEN modulating agent identified by a primary assay and may confirm that the modulating agent affects MPTEN in a manner relevant to the PTEN/IGF pathway. In some cases, MPTEN modulators will be directly tested in a secondary assay.

EX03-029P

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MPTEN polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MPTEN activity, and hence the PTEN/IGF pathway. The MPTEN polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

### **Primary Assays**

The type of modulator tested generally determines the type of primary assay.

#### ***Primary assays for small molecule modulators***

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (e.g., receptor-ligand binding), transcriptional activity (e.g., using a reporter gene), enzymatic activity (e.g., via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

EX03-029P

Cell-based screening assays usually require systems for recombinant expression of MPTEN and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MPTEN-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MPTEN protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MPTEN-specific binding agents to function as negative effectors in MPTEN-expressing cells), binding equilibrium constants (usually at least about  $10^7 \text{ M}^{-1}$ , preferably at least about  $10^8 \text{ M}^{-1}$ , more preferably at least about  $10^9 \text{ M}^{-1}$ ), and immunogenicity (e.g. ability to elicit MPTEN specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MPTEN polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MPTEN polypeptide can be full length or a fragment thereof that retains functional MPTEN activity. The MPTEN polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MPTEN polypeptide is preferably human MPTEN, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MPTEN interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MPTEN-specific binding activity, and can be used to assess normal MPTEN gene function.

Suitable assay formats that may be adapted to screen for MPTEN modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA,

EX03-029P

Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (*e.g.*, Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MPTEN and PTEN/IGF pathway modulators (U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,114,132 (phosphatase and protease assays), U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Proteases are enzymes that cleave protein substrates at specific sites. Exemplary assays detect the alterations in the spectral properties of an artificial substrate that occur upon protease-mediated cleavage. In one example, synthetic caspase substrates containing four amino acid proteolysis recognition sequences, separating two different fluorescent tags are employed; fluorescence resonance energy transfer detects the proximity of these fluorophores, which indicates whether the substrate is cleaved (Mahajan NP *et al.*, Chem Biol (1999) 6:401-409).

RNA folds into a myriad of tertiary structures that are responsible for its diverse functions in cells. In most instances, RNA is associated with RNA-binding proteins (RBPs) that protect, stabilize, package or transport RNA, mediate RNA interactions with other biomolecules or act catalytically on RNA. The structural information obtained for RNA alone and RNA-protein complexes has elucidated a variety of RNA tertiary structures and diverse modes for RNA-protein interaction. The specific interaction of proteins with highly structured RNAs makes it possible to target unique RNA motifs with small molecules, thus making RNA an interesting target for therapeutic intervention. Assays for RNA binding or processing may be based on homogeneous scintillation proximity (Liu J, *et al.*, Anal Biochem 2001 289:239-245), chemiluminescence (Mazumder A, Nucleic Acids Res 1998 26:1996-2000), gel shift (Stull RA, *et al.*, Antisense Nucleic Acid Drug Dev 1996 6:221-228; U.S. Pat. No: 6004749).

EX03-029P

Transcription factors control gene transcription. Electrophoretic mobility shift assay (EMSA) or gel shift assay is one of the most powerful methods for studying protein-DNA interactions. High throughput gel shift assays for transcription factors may involve fluorescence (Cyano dye Cy5) labeled oligodeoxynucleotide duplexes as specific probes and an automatic DNA sequencer for analysis (Ruscher K, et al., (2000) J Biotechnol 78:163-70). Alternatively high throughput methods involve colorimetric assays (Renard P, et al. (2001) Nucleic Acids Res 29(4):E21), or homogeneous fluorescence assays for the detection and quantification of sequence-specific DNA-binding proteins (Heyduk T, and Heyduk E (2001) Nat Biotechnol 20:171-6.)

Reductases are enzymes of oxidoreductase class that catalyze reactions in which metabolites are reduced. High throughput screening assays for reductases may involve scintillation (Fernandes PB. (1998) Curr Opin Chem Biol 2:597-603; Delaporte E et al. (2001) J Biomol Screen 6:225-231).

Assays for ATPase activity are known in the art, such as described in Blackburn et al (Blackburn CL, et al., (1999) J Org Chem 64:5565-5570). The ATPase assay is performed using the EnzCheck ATPase kit (Molecular Probes). The assays are performed using an Ultraspec spectrophotometer (Pharmacia), and the progress of the reaction are monitored by absorbance increase at 360 nm. Microtubules (1.7 mM final), kinesin (0.11 mM final), inhibitor (or DMSO blank at 5% final), and the EnzCheck components (purine nucleotide phosphorylase and MESG substrate) are premixed in the cuvette in a reaction buffer (40 mM PIPES pH 6.8, 5 mM paclitaxel, 1 mM EGTA, 5 mM MgCl<sub>2</sub>). The reaction is initiated by addition of MgATP (1 mM final).

High-throughput assays, such as scintillation proximity assays, for synthase enzymes involved in fatty acid synthesis are known in the art (He X et al (2000) Anal Biochem 2000 Jun 15;282(1):107-14).

**Apoptosis assays.** Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may

EX03-029P

further be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). An apoptosis assay system may comprise a cell that expresses an MPTEN, and that optionally has defective PTEN/IGF function (e.g. PTEN/IGF is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate PTEN/IGF modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate PTEN/IGF modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MPTEN function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MPTEN relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MPTEN plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

**Cell proliferation and cell cycle assays.** Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et al.*, 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [<sup>3</sup>H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [<sup>3</sup>H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation

EX03-029P

Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, *In Vitro Cell Dev Biol Anim* 34:239-46).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., *Molecular Cloning*, Cold Spring Harbor (1989)). For example, cells transformed with MPTEN are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) *Int J Radiat Biol Relat Stud Phys Chem Med* 49:237-55). Cells transfected with an MPTEN may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MPTEN, and that optionally has defective PTEN/IGF function (e.g. PTEN/IGF is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate PTEN/IGF modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate PTEN/IGF modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MPTEN function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MPTEN relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MPTEN plays a direct role in cell proliferation or cell cycle.

**Angiogenesis.** Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton



EX03-029P

Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MPTEN, and that optionally has defective PTEN/IGF function (e.g. PTEN/IGF is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate PTEN/IGF modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate PTEN/IGF modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MPTEN function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MPTEN relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MPTEN plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

**Hypoxic induction.** The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MPTEN in hypoxic conditions (such as with 0.1% O<sub>2</sub>, 5% CO<sub>2</sub>, and balance N<sub>2</sub>, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses an MPTEN, and that optionally has defective PTEN/IGF function (e.g. PTEN/IGF is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate PTEN/IGF modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary

EX03-029P

assay to test a candidate PTEN/IGF modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MPTEN function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MPTEN relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MPTEN plays a direct role in hypoxic induction.

**Cell adhesion.** Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells

EX03-029P

using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

**Tubulogenesis.** Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel™ (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4°C and forms a solid gel at 37°C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF- $\alpha$ . Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MPTEN's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF- $\alpha$ , ephrin, etc.

**Cell Migration.** An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell

EX03-029P

polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MPTEN's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

**Sprouting assay.** A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900 $\mu$ l of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100  $\mu$ l of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

EX03-029P

***Primary assays for antibody modulators***

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MPTEN protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MPTEN-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

***Primary assays for nucleic acid modulators***

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MPTEN gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MPTEN expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MPTEN) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MPTEN mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MPTEN protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MPTEN mRNA expression, may also be used to test nucleic acid modulators.

EX03-029P

### **Secondary Assays**

Secondary assays may be used to further assess the activity of MPTEN-modulating agent identified by any of the above methods to confirm that the modulating agent affects MPTEN in a manner relevant to the PTEN/IGF pathway. As used herein, MPTEN-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MPTEN.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MPTEN) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MPTEN-modulating agent results in changes in the PTEN/IGF pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the PTEN/IGF or interacting pathways.

### ***Cell-based assays***

Cell based assays may detect endogenous PTEN/IGF pathway activity or may rely on recombinant expression of PTEN/IGF pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

### ***Animal Assays***

A variety of non-human animal models of normal or defective PTEN/IGF pathway may be used to test candidate MPTEN modulators. Models for defective PTEN/IGF pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the PTEN/IGF

EX03-029P

pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, PTEN/IGF pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal PTEN/IGF are used to test the candidate modulator's affect on MPTEN in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MPTEN. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MPTEN is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, *Oncogene* 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MPTEN endogenously are injected in the flank,  $1 \times 10^5$  to  $1 \times 10^7$  cells per mouse in a volume of 100  $\mu$ L using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4%

EX03-029P

paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorigenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorigenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorigenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorigenicity and modulator efficacy can be evaluating life-span extension and/or



EX03-029P

tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

#### **Diagnostic and therapeutic uses**

Specific MPTEN-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the PTEN/IGF pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the PTEN/IGF pathway in a cell, preferably a cell pre-determined to have defective or impaired PTEN/IGF function (e.g. due to overexpression, underexpression, or misexpression of PTEN/IGF, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MPTEN activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the PTEN/IGF function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored PTEN/IGF function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired PTEN/IGF function by administering a therapeutically effective amount of an MPTEN -modulating agent that modulates the PTEN/IGF pathway. The invention further provides methods for modulating MPTEN function in a cell, preferably a cell pre-determined to have defective or impaired MPTEN function, by administering an MPTEN -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MPTEN function by administering a therapeutically effective amount of an MPTEN -modulating agent.

The discovery that MPTEN is implicated in PTEN/IGF pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the PTEN/IGF pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MPTEN expression occurs in a particular sample, including Northern blotting, slot blotting,

EX03-029P

ribonuclease protection, quantitative RT-PCR, and microarray analysis. (e.g., Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective PTEN/IGF signaling that express an MPTEN, are identified as amenable to treatment with an MPTEN modulating agent. In a preferred application, the PTEN/IGF defective tissue overexpresses an MPTEN relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MPTEN cDNA sequences as probes, can determine whether particular tumors express or overexpress MPTEN. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MPTEN expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MPTEN oligonucleotides, and antibodies directed against an MPTEN, as described above for: (1) the detection of the presence of MPTEN gene mutations, or the detection of either over- or under-expression of MPTEN mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MPTEN gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MPTEN.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MPTEN expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MPTEN expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein, including an antibody.

### EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

EX03-029P

### I. Drosophila PTEN/IGF screen

RNA interference (RNAi) was used to create dPTEN-deficient cultured *Drosophila* cells (Schneider S2 cells (Schneider, I. (1972) *J. Embryol. Exp. Morph.* 27, 363), adapted to serum-free media, from Invitrogen Corp., Carlsbad, CA). Cells were treated for 3 days with dPTEN double stranded RNA (dsRNA) or a control dsRNA representing sequences from a *Renilla luciferase* cDNA. After a 3 day dsRNA pretreatment, 1  $\mu$ M bovine insulin was added to cells treated with dPTEN dsRNA to provide additional stimulation of the IGF/insulin pathway. PTEN-deficient, insulin-stimulated cells and control cells were plated in 384-well format and dsRNA representing approximately 6000 different *Drosophila* genes were added to individual wells. A cell proliferation assay (AqueousOne™ assay – Promega Corp, Madison, WI) was used to quantify cell viability after 96-hours incubation. For each of the greater than 6000 dsRNA sequences tested in this manner, cell viability data was obtained on dPTEN-deficient, insulin-stimulated cells (insulin and dPTEN dsRNA-treated) and control cells (*Renilla luciferase* dsRNA-treated). Comparison of this data for each dsRNA identified dsRNA sequences that preferentially reduced the viability of insulin and dPTEN dsRNA treated cells.

### II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MPTEN symbol", and "MPTEN name aliases " provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MPTEN RefSeq\_NA or GI\_NA", "MPTEN GI\_AA", "MPTEN NAME", and "MPTEN Description" provide the reference DNA sequences for the MPTENs as available from National Center for Biology Information (NCBI), MPTEN protein Genbank identifier number (GI#), MPTEN name, and MPTEN description, all available from Genbank, respectively. The length of each amino acid is in the "MPTEN Protein Length" column.

EX03-029P

Names and Protein sequences of *Drosophila* modifiers of PTEN/IGF from screen (Example I), are represented in the "Modifier Name" and "Modifier GI\_AA" column by GI#, respectively.

Table 1

MPTEN symbol	MPTEN name aliases	MPTEN RefSeq_NA or GI_NA	MPTEN GI_AA	MPTEN NAME	MPTEN Description	MPTEN Protein Length	Modifier Name	Modifier GI_AA
CNO17	CNOT7   CAF1   hCAF-1   BTG1 binding factor 1   carbon catabolite repressor protein (CCR4)-associative factor 1   CCR4-NOT transcription complex, subunit 7	NM_013354   NM_054026	7019339	CCR4-NOT transcription complex, subunit 7	poly(A)-specific ribonuclease; signal transducer; transcription cofactor; transcription factor; transcription factor	262	CG5684	21357541
CNOT8	CNOT8   CAF1   POP2   CALIF   hCAF1   POP2 (yeast homolog)   PGK promoter directed over production   CCR4-NOT transcription complex, subunit 8	NM_004779	24496778	CCR4-NOT transcription complex, subunit 8	transcription factor	292	CG5684	21357541

EX03-029P

COPA	COPA   HEP-COP   xenon   alpha coat protein   coatamer protein complex, subunit alpha	NM_004371	4758030	coatamer protein complex, subunit alpha	RNA binding; intracellular transporter	1224	alphaCop	24655452
FASN	FASN   FAS   OA-519   MGC14367   MGC15706   fatty acid synthase	NM_004104	21618359	fatty acid synthase	acyl-CoA thioesterase II; acyl carrier; enoyl-[acyl- carrier protein] reductase; fatty-acid synthase; fatty-acid synthase	2509	BcDNA:G H07626	19920632
HSPA9B	HSPA9B   CSA   MOT   MOT2   GRP75   HSPA9   PBP74   mot-2   MGC4500   MTHSP75   mthsp75   p66-mortalin   mortalin, perinuclear   heat shock 70kD protein 9   peptide- binding protein 74   75 kDa glucose regulated protein   stress-70 protein, mitochondri al   heat shock 70kDa protein 9B (mortalin-2)	NM_004134	24234688	heat shock 70kDa protein 9B (mortalin-2)	chaperone	679	Hsc70-5	24653595

EX03-029P

LOC344510	LOC344510   similar to Stress-70 protein, mitochondrial precursor (75 kDa glucose regulated protein) (GRP 75) (Peptide-binding protein 74) (PBP74) (Mortalin) (MOT)   na	XM_293066	29732424	similar to Stress-70 protein, mitochondrial precursor (75 kDa glucose regulated protein) (GRP 75) (Peptide-binding protein 74) (PBP74) (Mortalin) (MOT)	na	529	Hsc70-5	24653595
KIAA1007	KIAA1007   AD-005   adrenal gland protein AD-005   KIAA1007 protein	NM_016284	20521724	KIAA1007 protein	transcription regulator	1835	CG1884	24652112
KIAA1604	KIAA1604   KIAA1604 protein	XM_034594	10047283	KIAA1604 protein	na	937	CG12750	24584968
FKSG17	FKSG17	NM_032031	14042953	FKSG17	nucleic acid binding; nucleic acid binding	213	Nacalpa	19549608
KIAA0363	KIAA0363   KIAA0363 protein	XM_166571	2224667	KIAA0363 protein	na	1522	Nacalpa	19549608
LOC152682	LOC152682   similar to nascent-polypeptide-associated complex alpha polypeptide [Homo sapiens]   na	XM_087502	18557511	similar to nascent-polypeptide-associated complex alpha polypeptide [Homo sapiens]	na	215	Nacalpa	19549608

NACA	NACA   nascent-polypeptide-associated complex alpha polypeptide	NM_005594	5031931	nascent-polypeptide-associated complex alpha polypeptide	nucleic acid binding	215	Nacalpa	19549608
PMPCB	PMPCB   MPPB   MPP11   MPPP52   mitochondrial processing peptidase-beta   peptidase (mitochondrial processing) beta	NM_004279	4758734	peptidase (mitochondrial processing) beta	beta-mitochondrial processing peptidase	489	CG3731	24646943
UQCRC1	UQCRC1   D3S3191   ubiquinol-cytochrome c reductase core protein I	NM_003365	4507841	ubiquinol-cytochrome c reductase core protein I	electron transporter; ubiquinol-cytochrome c reductase	480	CG3731	24646943
POM121	POM121   MGC3792   KIAA0618   DKFZP586G1822   DKFZP586P2220   P145   nuclear pore membrane protein 121 kDa   nuclear envelope pore membrane protein POM121   POM121 membrane glycoprotein (rat)	NM_172020	26051278	POM121 membrane glycoprotein (rat)	na	984	CG14712	21356627

EX03-029P

PSMA2	PSMA2   MU   HC3   PSC2   PMSA2   macropain subunit C3   proteasome subunit HC3   proteasome component C3   multicatalytic endopeptidase complex subunit C3   proteasome (prosome, macropain) subunit, alpha type, 2	NM_002787	4506181	proteasome (prosome, macropain) subunit, alpha type, 2	na	234	Pros25	17737927
PSMA3	PSMA3   HC8   PSC3   MGC123062   MGC32631   macropain subunit C8   proteasome subunit C8   multicatalytic endopeptidase complex subunit C8   proteasome (prosome, macropain) subunit, alpha type, 3	NM_002788 NM_15213	4506183	proteasome (prosome, macropain) subunit, alpha type, 3	na	255	Prosalpha 7	24652204



EX03-029P

PSMB1	PSMB1   HC5   PSC5   PMSB1   FLJ25321   macropain subunit C5   proteasome gamma chain   proteasome subunit HC5   proteasome component C5   multicatalytic endopeptidase complex subunit C5   proteasome (prosome, macropain) subunit, beta type, 1	NM_002793	4506193	proteasome (prosome, macropain) subunit, beta type, 1	peptidase	241	Pros26	17737605
LOC221890	LOC221890   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_167259	20539647	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	257	Pros26.4	24649446
LOC285213	LOC285213   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_210528	27479738	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	241	Pros26.4	24649446

EX03-029P

LOC343928	LOC343928   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_292848	29727184	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	419	Pros26.4	24649446
LOC345645	LOC345645   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_293923	29736610	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	415	Pros26.4	24649446
LOC345986	LOC345986   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_294034	29740164	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	233	Pros26.4	24649446
LOC346682	LOC346682   similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]   na	XM_294368	29737532	similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]	na	366	Pros26.4	24649446

EX03-029P

PSMC1	PSMC1   S4   p56   P26S4   MGC8541   MGC24583   26S protease regulatory subunit 4   proteasome 26S subunit, ATPase, 1   proteasome (prosome, macropain) 26S subunit, ATPase, 1	NM_002802	24430151	proteasome (prosome, macropain) 26S subunit, ATPase, 1	proteasome ATPase; proteasome ATPase; proteasome ATPase; proteasome ATPase; protein binding; poly- glutamine tract binding	440	Pros26.4	24649446
PSMD2	PSMD2   S2   P97   TRAP2   MGC14274   55.11 protein   TNFR- associated protein 2   26S proteasome subunit p97   26S proteasome regulatory subunit S2   26S proteasome non-ATPase regulatory subunit 2   tumor necrosis factor receptor- associated protein 2   proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	NM_002808	25777602	proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	protein binding; proteasome activator	908	Rpn1	21356859

EX03-029P

RANBP2	RANBP2   NUP358   P270   nucleoporin 358   nuclear pore complex protein Nup358   RAN binding protein 2	NM_006267	6382079	RAN binding protein 2	RAN protein binding; SUMO ligase	3224	CG11856	24649980
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### III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MPTEN peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MPTEN activity.

### IV. High-Throughput In Vitro Binding Assay.

<sup>33</sup>P-labeled MPTEN peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl<sub>2</sub>, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate PTEN/IGF modulating agents.

### V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins,  $3 \times 10^6$  appropriate recombinant cells containing the MPTEN proteins are plated on 10-cm dishes and transfected on the

EX03-029P

following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at  $15,000 \times g$  for 15 min. The cell lysate is incubated with 25  $\mu$ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

#### VI. Kinase assay

A purified or partially purified MPTEN is diluted in a suitable reaction buffer, e.g., 50 mM Hepes, pH 7.5, containing magnesium chloride or manganese chloride (1-20 mM) and a peptide or polypeptide substrate, such as myelin basic protein or casein (1-10  $\mu$ g/ml). The final concentration of the kinase is 1-20 nM. The enzyme reaction is conducted in microtiter plates to facilitate optimization of reaction conditions by increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100  $\mu$ l. The reaction is initiated by the addition of  $^{33}\text{P}$ -gamma-ATP (0.5  $\mu$ Ci/ml) and incubated for 0.5 to 3 hours at room temperature. Negative controls are provided by the addition of EDTA, which chelates the divalent cation ( $\text{Mg}^{2+}$  or  $\text{Mn}^{2+}$ ) required for enzymatic activity. Following the incubation, the enzyme reaction is quenched using EDTA. Samples of the reaction are transferred to a 96-well glass fiber filter plate (MultiScreen, Millipore). The filters are subsequently washed with phosphate-buffered saline, dilute phosphoric acid (0.5%) or other suitable medium to remove excess radiolabeled ATP. Scintillation cocktail is added to the filter plate and the incorporated radioactivity is quantitated by scintillation counting (Wallac/Perkin Elmer). Activity is

EX03-029P

defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

#### VII. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardaïs, Genome Collaborative, and Ambion.

TaqMan analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed using a 7900HT instrument.

Taqman reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis is prepared using a universal pool of human cDNA samples, which is a mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal

EX03-029P

pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the standard deviation of all normal samples (i.e.,  $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$  ).

A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

EX03-029P

**WHAT IS CLAIMED IS:**

1. A method of identifying a candidate PTEN/IGF pathway modulating agent, said method comprising the steps of:
  - (a) providing an assay system comprising a MPTEN polypeptide or nucleic acid;
  - (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and
  - (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate PTEN/IGF pathway modulating agent.
2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MPTEN polypeptide.
3. The method of Claim 2 wherein the cultured cells additionally have defective PTEN/IGF function.
4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MPTEN polypeptide, and the candidate test agent is a small molecule modulator.
5. The method of Claim 4 wherein the assay is a binding assay.
6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.
7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MPTEN polypeptide and the candidate test agent is an antibody.



EX03-029P

8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MPTEN nucleic acid and the candidate test agent is a nucleic acid modulator.
9. The method of claim 8 wherein the nucleic acid modulator is an antisense oligomer.
10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.
11. The method of Claim 1 additionally comprising:
  - (d) administering the candidate PTEN/IGF pathway modulating agent identified in (c) to a model system comprising cells defective in PTEN/IGF function and, detecting a phenotypic change in the model system that indicates that the PTEN/IGF function is restored.
12. The method of Claim 11 wherein the model system is a mouse model with defective PTEN/IGF function.
13. A method for modulating a PTEN/IGF pathway of a cell comprising contacting a cell defective in PTEN/IGF function with a candidate modulator that specifically binds to a MPTEN polypeptide, whereby PTEN/IGF function is restored.
14. The method of claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in PTEN/IGF function.
15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.
16. The method of Claim 1, comprising the additional steps of:

EX03-029P

(d) providing a secondary assay system comprising cultured cells or a non-human animal expressing MPTEN ,

(e) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

(f) detecting an agent-biased activity of the second assay system,

wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate PTEN/IGF pathway modulating agent,

and wherein the second assay detects an agent-biased change in the PTEN/IGF pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.

18. The method of Claim 16 wherein the secondary assay system comprises a non-human animal.

19. The method of Claim 18 wherein the non-human animal mis-expresses a PTEN/IGF pathway gene.

20. A method of modulating PTEN/IGF pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MPTEN polypeptide or nucleic acid.

21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermned to have a pathology associated with the PTEN/IGF pathway.

22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.

23. A method for diagnosing a disease in a patient comprising:

EX03-029P

- (a) obtaining a biological sample from the patient;
- (b) contacting the sample with a probe for MPTEN expression;
- (c) comparing results from step (b) with a control;
- (d) determining whether step (c) indicates a likelihood of disease.

24. The method of claim 23 wherein said disease is cancer.

EX03-029P

**ABSTRACT OF THE DISCLOSURE**

Human MPTEN genes are identified as modulators of the PTEN/IGF pathway, and thus are therapeutic targets for disorders associated with defective PTEN/IGF function. Methods for identifying modulators of PTEN/IGF, comprising screening for agents that modulate the activity of MPTEN are provided.

EX03-029P

# Nucleic Acid and Polypeptide sequences

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complex, subunit 7 (CNOT7), transcript variant 1, mRNA
GGCACGAGGGGAGCAGCAGGTGCGGCGCAGCTCCTGCTCGCCTTCCCTTCGCTGGGCGAGAGGTGTCTATG
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EX03-029P

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>gi|6996002|ref|NM\_004371.2| Homo sapiens coatomer protein complex,  
 subunit alpha (COPA), mRNA

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EX03-029P

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>gi|21618358|ref|NM\_004104.3| Homo sapiens fatty acid synthase (FASN), mRNA

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EX03-029P

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EX03-029P

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>gi|24234687|ref|NM\_004134.3| Homo sapiens heat shock 70kDa protein 9B  
(mortalin-2) (HSPA9B), nuclear gene encoding mitochondrial protein,  
mRNA

EX03-029P

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>gi|30150447|ref|XM\_293066.2| Homo sapiens similar to Stress-70  
 protein, mitochondrial precursor (75 kDa glucose regulated protein)  
 (GRP 75) (Peptide-binding protein 74) (PBP74) (Mortalin) (MOT)  
 (LOC344510), mRNA

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EX03-029P

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>gi|7706213|ref|NM\_016284.1| Homo sapiens KIAA1007 protein (KIAA1007),  
 mRNA

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>gi|27479970|ref|XM\_034594.7| Homo sapiens KIAA1604 protein (KIAA1604),  
 mRNA

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EX03-029P

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>gi|14042952|ref|NM\_032031.1| Homo sapiens FKSG17 (FKSG17), mRNA  
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EX03-029P

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>gi|20541583|ref|XM\_166571.1| Homo sapiens KIAA0363 protein (KIAA0363),  
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EX03-029P

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>gi|27481387|ref|XM\_087502.6| Homo sapiens similar to alpha NAC/1.9.2.  
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>gi|5031930|ref|NM\_005594.1| Homo sapiens nascent-polypeptide-  
 associated complex alpha polypeptide (NACA), mRNA  
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>gi|4758733|ref|NM\_004279.1| Homo sapiens peptidase (mitochondrial  
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EX03-029P

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>gi|4507840|ref|NM\_003365.1| Homo sapiens ubiquinol-cytochrome c  
 reductase core protein I (UQCRC1), mRNA

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EX03-029P

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>gi|26051277|ref|NM_172020.1| Homo sapiens POM121 membrane glycoprotein
(rat) (POM121), mRNA
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EX03-029P

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>gi|23110936|ref|NM\_002787.2| Homo sapiens proteasome (prosome,  
macropain) subunit, alpha type, 2 (PSMA2), mRNA  
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>gi|23110937|ref|NM\_002788.2| Homo sapiens proteasome (prosome,  
macropain) subunit, alpha type, 3 (PSMA3), transcript variant 1, mRNA  
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EX03-029P

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>gi|22538462|ref|NM\_002793.2| Homo sapiens proteasome (prosome, macropain) subunit, beta type, 1 (PSMB1), mRNA  
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>gi|30152230|ref|XM\_167259.2| Homo sapiens similar to protease (prosome, macropain) 26S subunit, ATPase 1 (LOC221890), mRNA  
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ACTTGA

>gi|27479737|ref|XM\_210528.1| Homo sapiens similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus] (LOC285213), mRNA  
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>gi|29727183|ref|XM\_292848.1| Homo sapiens similar to protease (prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus] (LOC343928), mRNA  
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EX03-029P

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>gi|29736609|ref|XM\_293923.1| Homo sapiens similar to protease  
(prosome, macropain) 26S subunit, ATPase 1 (LOC345645), mRNA  
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>gi|29740163|ref|XM\_294034.1| Homo sapiens similar to protease  
(prosome, macropain) 26S subunit, ATPase 1 [Rattus norvegicus]  
(LOC345986), mRNA  
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>gi|29737531|ref|XM\_294368.1| Homo sapiens similar to protease  
(prosome, macropain) 26S subunit, ATPase 1 (LOC346682), mRNA  
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EX03-029P

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>gi|24430150|ref|NM\_002802.2| Homo sapiens proteasome (prosome,  
macropain) 26S subunit, ATPase, 1 (PSMC1), mRNA  
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>gi|25777601|ref|NM\_002808.3| Homo sapiens proteasome (prosome,  
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EX03-029P

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>gi|19718756|ref|NM\_006267.3| Homo sapiens RAN binding protein 2  
 (RANBP2), mRNA

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EX03-029P

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EX03-029P

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>gi|7019339|ref|NP\_037486.1| CCR4-NOT transcription complex, subunit 7  
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8; PKG promoter directed over production; POP2 (yeast homolog) [Homo  
sapiens]  
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EX03-029P

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 HMYLSSFVLAEKAAAYRDRDSQRDLVEAVAHILGIRDLA AVNLDSSSLADLGLDSLMSVEVRQTLERELNL  
 VLSVREVRQTLRLKLQELSSKADEASELACPTPKEDGLAQQTQLNLRSLLVNPEGPTLMRLNSVQSSER  
 PLFLVHPHIEGSTTVFHSLSRLSIPTYGLQCTRAAPLDSIHS LAAYYIDCIRQVQPEGPYRVAGYSYGAC  
 VAFEMCSQLQAQSQSPAPTHNSLFLFDGSPTYVLA YTSYRAKLT PGCEAEAEAEICFFVQQTDM EHN  
 VLEALLPLKGLEERVAAVDLI IKSHQGLDRQELSFAARSFYKLRAAEQYTPKAKYHGNVMLLRKTGG  
 AYGEDLGADYNLSQVCDGKVS VHVIEGDHRTLLESGSLESIISIIHSSLAEPVSVREG

>gi|24234688|ref|NP\_004125.3| heat shock 70kDa protein 9B precursor;  
 heat shock 70kD protein 9; stress-70 protein, mitochondrial; 75 kDa  
 glucose regulated protein; peptide-binding protein 74; mortalin,  
 perinuclear; p66-mortalin [Homo sapiens]  
 MISASRAAAARLVGAAASRGPTAARHQDSWNGLSHEAFRLVSRRDYASEAIKGA VVGIDLGTNTSCVAVM  
 EGKQAKVLENAEGARTTPSVVAFTADGERLVGMPAKRQAVTNPNNTFYATKRLIGRRYDDPEVQKDIKNV  
 PFKIVRASNGDAWVEAHGKLYSPSQIGAFVLMKMKETAENYLGH TAKNAVITVPAYFNDSQRQATKDAGQ  
 ISGLNVLRVINEPTAAALAYGLDKSEDKVIAVYDLGGGTFDISILEIQKGVFEVKSTNGDTFLGGEDFDQ  
 ALLRHIVKEFKRETGVDLTKDNMALQVRREAAEKAKCELS SVQTDINLPYLTMDSGPKHLNMKLTRAQ  
 FEGIVTDLIRRTIAPCQKAMQDAEVSKSDIGEVLVGGMTRMPKVQQTVDLFG RAPSKAVNPDEAVAIG  
 AAIQGGVLAGDVTVDVLLDVTPLSLGIETLGGVFTKLINRNTTIPTKKSQVFSTAADGQTQVEIKVCQGE  
 REMAGDNKLLGQFTLIGIPPAPRGVPQIEVTFDIDANGIVHVS AKDKGTGREQQIVIQSSGGLSKDDIEN  
 MVKNAEKYAEEDRRKKERVEAVNMAEGIIHDTETKMEEFKDQLPADECNKLKEEISKMRELLARKDSETG  
 ENIRQAASSLQQA SKLFEMAYKKMASEREGSGSSCTGEQKEDQKEEKQ

>gi|29732424|ref|XP\_293066.1| similar to Stress-70 protein,  
 mitochondrial precursor (75 kDa glucose regulated protein) (GRP 75)  
 (Peptide-binding protein 74) (PBP74) (Mortalin) (MOT) [Homo sapiens]  
 MCDKAAIISASRAAAARLRGTAASPGPTAARQQD GWNGLSHEAFRIVSRQDYASEAINGAAGGVYLGTTN  
 SCVAVMEGKQAKVLENAEGARTTPSVVAFTADVQKDIKNIPFKIVCASNGDAWVEAHGKLYSPSQIGAFV  
 SMKMKETAENYLGH TAKNAVIAVPAYFNDLQRQATKDAGQISGLNVLRVINEPTAAALAYGLDKSKDKVI

EX03-029P

AVYDLGGGTFDISILEFQKGVFEVKSTNGDTFLGGEDFDQALLQHIVKEFKRETGVDLTKDNVAFQRVWE  
AAEKAKCELSSSVQTDINLPYLTMDSGPKHLNKLTHAQFEGIVTDLIRRTIAPCQKAMQDAEVSKSDI  
GEVILVEPPSKAVNPDEAVAIGAAIQGDVLADVDVLLLDVILPLSLGIETLRGVFTKLINRNTTIPTKK  
SQVFSTAADGQTQVEIKVCQGEREMAGDNKLLGQFTLIGIPPAPRGVPQIKVTFDIDANGIIHVSADKDG  
TGHEQQIIVIQSSGGLSKDDVENMVKNAEKYAKEDQRRKE

>gi|20521724|dbj|BAA76851.2| KIAA1007 protein [Homo sapiens]  
LIMHAMAENYMRGEQYDQAKLSRILDVAQDLKALSMLNGTPFAFVIDLAALASRREYLKLDKWLTDKIR  
EHGEPFIQACMTFLKRRCPSELGGLAPEKDQPKSAQLPPETLATMLACLQACAGSVSQELSETILTMVAN  
CSNMVNKARQPPPGVMKGRPPSASSLDAISPVQIDPLAGMTSLSIGGSAAPHTQSMQGFPPNLGSAFST  
PQSPAKAFPLSTPNQTTAFSGIGGLSSQLPVGGLGTGSLTGIGTGALGLPAVNNDPFVQRKLGTSGLNQ  
PTFQQTDLSSQWPEANQHFKEIDDEANSYFQRIYNHPPHPTMSVDEVLEMLQRFKDKSTIKREREVPNCM  
LRNLFEEYRFFPQYPDKELHITACLFGGIIEKGLVTYMALGLALRYVLEALRKPFSGKMYFYGIAALDRF  
KNRLKDYPPQYCOHLASISHFMQFPHHLQVEYIEYGCQSRDPPVKMQGSITTPGSIALAQAQAQAVPAKAP  
LAGQVSTMVTSTTTTTVAKTVTVTRPTGVSFKQDVPPSINTTNIDTLLVATDQTERIVEPPENIQEKIAP  
IFNNLSQSNMTQKVEELKETVKEEFMPWVSQYLVMKRVSIENPNFSLYSNFDLTKNPEFNKMLVNETYR  
NIKVLLTSDKAAANFSDRSLLKNLGHWLGMITLAKNKPILHTDLDVKSLLLEAYVKGQQLLYVVPFVAK  
VLESSIRSVPFRPPNPWTMAIMNVLAELHQEHDLKLNLFIEVLCKNLALDINELKPGNLLKDKDRLLKN  
LDEQLSAPKDKVQPEELPPIITTTTTSTTTPATNTTCTATVPPQPYSYHDINVYSLAGLAPHITLNPITP  
LFQAHPLKQCVRAIERAVQELVHPVVDRSIKIAMTTCEQIVRKDFALDSEESRMRIAHHMMRNLTAG  
MAMITCREPILLMSISTNLKNSFASALRTASQQREMMQAAAQLAQDNCELACCFIQKTAVEKAGPEMDK  
RLATEFELRKHARQEGRRYCDPVVLTQYQARMPEQIRLKVGGVDPKQLAVYEEFARNVPGFLPTNDLSQP  
TGFLAQPMQAWATDDVAQIYDKCITELEQLHLAIPPTLAMNPQAALRSLEVVVLSRNSRDAIAALGL  
LQKAVEGLLDATSGADADLLRYRECHLLVLKALQDGRAYGSPWCNKQITRCLIECRDEYKYNVEAVELL  
IRNHLVNMQQYDLHLAQSMENGLNYMAVAFAMQLVKILLVDERSVAHVTEADLFHTIETLMRINAHSRGN  
APEGLPQLMEVVRSNYEAMIDRAHGGPNFMHSGISQASEYDDPPGLREKAEYLLREWVNLVHSAAGRD  
STKAFSAFVGQMQHQQGILKTDLLITRFRCLCTEMCEVISYRAQAEQQHNPANPTMIRAKCYHNLDAFVR  
LIALLVKHSGEATNTVTINLLNKVLGIVVGVLLQDHDVRQSEFQQLPYHRIFIMLLLELNAPEHVELETI  
NFQTLTAFNCSTFHILRPTKAPGFVYAWLELISHRIFIARMLAHTPQQKGWPMYAQLLIDLFKYLAFLPLRN  
VELTKPMQILYKGTLRVLLVLLHDFPEFLCDYHYGFCDVIPPNCIQLRNLIILSAFPRNMRLPDPFTPNLK  
VDMLSEINIAPRILTNFTGVMPPQFKKDLDSYLKTRSPVTFLSDLRSNLQVSNEPGNRYNLQINALVLY  
VGTQAIHAIHNGSTPSMSTITHSAHMDIFQNLAVDLDTGGRYLFNLAIANQLRYPNSSHYFSCTMLYL  
FAEANTEAIEQETRVLLERLIVNRPHPWGLLITFIELIKNPAFKFWNHEFVHCAPEIEKLFQSVQAQCCM  
GQKQAQVMEGTGAS

>gi|10047283|dbj|BAB13430.1| KIAA1604 protein [Homo sapiens]  
TVKEFRALGTCYLDQFEASLIYWTNWQQKMKSSVAQIKPSSGHDRENLSYQRNSSPEDRYEEQERSPR  
DRDYFDYSRSDYHSRRGRSYDSSMESRNRDREKRRERERDTRKRSRKSPSPGRRNPETSVTQSSSAQD  
EPATKKKKDELDPLLTRTGAYIPPAKLMMQEQTIDKNSLAYQRMSWEALKKSINGLINKVNIISNISII  
IQELLQENIVRGRGILLSRSVLQAQASPIFTHVYAALVAIINSKFPQIGELILKRLILNFRKGYRRNDKQ  
LCLTASKFVAHLINQNVAVEVLCLEMLTLLERPTDSDVEVAIGFLKECGLKLTVQSPRGINAIFERLRN  
ILHESEIDKRVQYMIEMFAVRKDGFKDHPIILEGLDLVEEDDQFTHMLPLEDDYNPEDVLNVFKMDPNF  
MENEKYKAIKKEILDEGDTSDNTDQDAGSSEDEEEEEEGEEDDEGQKVTHDKTEINLVSFRTIYL  
AIQSSLDFECAHKLKMEFPESQTKELCNMILDCCAQORTYEFKFFGLLAGRFCMLKKEYMESFEGIFKE  
QYDTIHRLETNKLRLNVAKMFALLTYDLSLPSVLECIKLSBETTTSSSRIFVKIFFQELCEYMGLPKLNA  
RLKDETLQPFEGELLPRDNPRNTRFAINFFTSIGLGLTDELREHLKNTPKVIVAQKPDVEQNKSSPSSS  
SSASSSSSDSDSDSDSDSSSESSSESSSDSSSISSSSASANDVRKKGHGKTRSKVEVDKLRNQQTND  
RKQKERRQEHGHQETRTERERRSEKHRDQNSGNSWRDPITKYTSDKDVPSERNYSRVANDRDQEMHID  
LENKHGDPKKKRGERRNSFSENEKHTRIKDSENFRKDRSKSKEMNRKHSGRSDEDRYQNGAERRWEK  
SSRYSEQSRESKKNQDRRREKSPAKQK

>gi|14042953|ref|NP\_114420.1| FKSG17 [Homo sapiens]  
MPGEATETVPAIEQQLLPQAETGSGTESDSDESVPLEEQDSTQVTAQVQLVVAEIDEEPVSKAQRR  
SEKKARKARFKLGLQQVTGVTRVTIRKSKNLFVITKPDVYKSPASDTYMFGEAKIEDLSQEAQLAAAE  
KFKVQGEAVSNIQENTQPTVQEGSEDEEVDETGVEIKDIELVLSQANVWGAKAVRALKNSNDIVNAIME  
LTM

EX03-029P

>gi|2224667|dbj|BAA20818.1| KIAA0363 [Homo sapiens]  
 EPCALTPGSPSHLALTFPLPSKPGARPQPEGASWDAGPGGAPSAWADPGEGGSPMLLPEGLSSQALSTEAP  
 LPATLEPRIVMGEETCQALLSPRAARTALRDQEGGHASDPDPPELCSQGDLSVPSPPPDPDSFPTTPSTP  
 TKTTYALLPACGPHGDARDSEALRDELLDSPASPSPSGSYTADGDSWASSPSCSLSLAPAEGLDFPSG  
 WGLSPQSGMVDERELHPAGTPEPPSSSESLADSSSSWGQEGHFFDLDFLANDPMIPAALLPFQGSILIFQ  
 VEAVEVTPLSPEEEEEAVADPDGGLAGEGEEDSTSASFLQSLSDLSITEGMDEAFRRDTSAASSD  
 SDSASYAEADDERLYSGEPHAQATLLQDSVQKTEESGGGAKGLQAQDGTVSWAVEAAPQTSRGRAYLSQ  
 RQELISEVTEBGLALQESTATVTPHTLQVAPGLQVEVATRVTPQAGEEETDSTAGQESAAMAMPQPSQE  
 GISEILGQESVTAELPTPQEETSLTCLPDSQNLKEEGGLDLPGRKPVAATIVPRQAKEDLTLPQDS  
 AMTPPLPLQDSDLSSAPKPVAAATIVSQAEGLTLPQDSVMTPLPLQDTELSSAPKPVAAATLVSSQA  
 EEGLTLPQDSAMTPPLPLQDSDLSSAPKPVAAATLVSSQAEEGLTLPQDSAMTPPLPLQDSDLSSAPKPV  
 AAATLVSSQAEEGLTLPQDSAMTPPLPLQDSDLSSAPKPVAAATIVSQAEGLTLPQDSAMTPPLPLQD  
 TDLSSAPKPVAAATIVSQAEGLTLPQDSAMTPPLPLQDSDLSSAPKPVAAATPVSSQAEEGLTLPQDS  
 AMTPPLPLQDSDLSSAPKPVAAATPVSSQAEEGLTLPQDSAMTAPLPLQDTGPTSGPEPLAVATPQTQLQA  
 EAGCAPGTEPVATMAQVEVGEALGFRPAPEEKNAALPTVPEPAALDQVQDDPQPAEAGTPWAAQEDAD  
 STLGMELSLPEPASGAGEEIAEALSRPGREACLEARAHTGDGAKPDSQKETLEVENQQEGGLKLLAQE  
 HGPRALGGAREVDPDAPPAACEVPSQARLLSPAREERGLSGKSTPEPTLPSAVATEASLDSCPESSVAV  
 SSLDRGCPDAPAPTSAPTSQQPEPVLGLSVEQPHEVPSVLGTPLLQPPENLAKGQSTPVDRLGPDPS  
 APGTLAGAALPPEPPAPCLCQDPQEDSVEDEEPPGSLGLPPPQAGVQPAAAAVSGTTQPLGTGPRVSL  
 PHSPLLSPKVASMDAKDLALQILPPCQVPPPSGPGSPAGPQGLSAPEQQEDEDSEEDSPRALGSGQHSD  
 SHGESSAELDEQDILAPQTVQCPAQAPAGGSEETIAKAKQSRSEKKARKAMSKLGLRQIQGVTRITIQKS  
 KNILFVIAKPDVFKSPASDTYVVFGEAKIEDLSQQVHKAAAEKFKVPSEPSALVPESAPRPRVRLCKEE  
 EEEEEVDEAGLELRDIELVMAQANVSRAKAVRALRDNHSDIVNAIMELTM

>gi|18557511|ref|XP\_087502.1| similar to alpha NAC/1.9.2. protein [Homo sapiens]  
 MPCEATETVPATEQELPQPQAEETGSGTESDSDESVPPEEQDSTQSTQEAQLVAAAEEIDEEPVSQAKQI  
 WSEKKAQKAMSKLGLRQVTGVTRVAIRKSKNILFVITKPNVCKSPALDITYIVSGEAKIEDLSEQAQLAA  
 EKFNVQGEAVSNIQENTQTPTVQKESEEEVDETGVVVKDIELVMSQANVWRKAVHALKNNSNDIVSAI  
 MELTM

>gi|5031931|ref|NP\_005585.1| nascent-polypeptide-associated complex  
 alpha polypeptide [Homo sapiens]  
 MPGEATETVPATEQELPQPQAEETGSGTESDSDESVPPEEQDSTQATTQQAQLAAAAEIDEEPVSQAKQS  
 RSEKKARKAMSKLGLRQVTGVTRVTIRKSKNILFVITKPDVYKSPASDTYIVFGEAKIEDLSQAQLAA  
 EKFKVQGEAVSNIQENTQTPTVQKESEEEVDETGVVVKDIELVMSQANVSRKAVRALKNNSNDIVNAI  
 MELTM

>gi|4758734|ref|NP\_004270.1| peptidase (mitochondrial processing) beta;  
 mitochondrial processing peptidase-beta [Homo sapiens]  
 MAAAAARVVLSSAARGGLWGFSESLIRGAAGRSYLFGENRLRSTQAAQVVLNVPETRVTCLESLRVA  
 SEDSGLSTCTVGLWIDAGSRYENENKNGTAHFLEHMAFKGTKKRSQDLLELEIENMGAHLNAYTSREQTV  
 YYAKAFSKDLPRAVEILADIIONSTLGEAEIERERGVILREMGEVETNLQEVVFDYLHATAYQNTALGRT  
 ILGPTENIKSISRKDLVDYITTHYKGPRIVLAAAGGVSHDELLDLAKFHFGDSLCTHKGEIPALPPCKFT  
 GSEIRVRDDKMPLAHLAIAVEAVGWAHPDTICLMVANTLIGNWDRSFGGGMNLSKLAQLTCHGNLCHSF  
 QSFNTSYTDTGLWGLYMVCESSTVADMLHVQKEWMRLCTSVTESEVARARNLLKTNMLLQLDGSTPICE  
 DIGRQMLCYNRRIPPELEARIDAVNAETIREVCTKYIYNRSPAIAAVGPIKQLPDFKQIRSNMCWLRD

>gi|4507841|ref|NP\_003356.1| ubiquinol-cytochrome c reductase core  
 protein I [Homo sapiens]  
 MAASVVCRAATAGAQLLRARRSPALLRTPALRSTATFAQALQFVPETQVSLDNLGRVASEQSSQPTCT  
 VGVWIDVGSRFETEKNNAGYFLEHLAFKGTKNRPGSALEKEVESMGHLNAYSTREHTAYYIKALSKDL  
 PKAVELLGDIVQNCSEDSQIEKERDVLREMQENDASMRDVVFNYLHATAFQGTPLAQAVEGSPSENVK  
 LSRADLTEYLSHYKAPRMVLAAGGVEHQQLDLAQKHLGGIPWYAEADAVPTLTPCRFTGSEIRHRDD  
 ALPPAHVAIAVEGPGWASPDVALQVANAIIGHYDCTYGGGVHLSSPLASGAVANKLCQSFQTFISICYAE  
 TGLLGAHFVCDRMKIDDMFVLQGWMLCTSATSEVARGKNILRNALVSHLDGTPVCEDIGRSLTY  
 GRRIPLAEWESRIAEVDASVREICSKYIYDQCPAVAGYGPIEQLPDYNIRSGMFWLRF

EX03-029P

>gi|26051278|ref|NP\_742017.1| nuclear pore membrane protein 121;  
 nuclear pore membrane protein 121 kDa; nuclear envelope pore membrane  
 protein POM 121; P145 [Homo sapiens]  
 MVCSPVTVRIAPPDRRFRSAIPEQIISSTLSSPSSNAPDPCAKETVLSALKEKEKKRTVEEEDQIFLDG  
 QENKRRRHDS SSGHSAFELVANGVPASFV PKPSLKRGLNSQSSDDHLNKRSSSSMSSLTGAYASGI  
 PSSSRNAITSSYSSTRGISQLWKRNGPSSSPFSSPASSRSQTPERPAKKIREEEELCHHSSSSTPLAADRE  
 SQGEKAADTTTPRKQNSNSQSTPGSSGQRRKRVQLLPSRRGEQLTLPPPPQLGYSSITAEDLDLEKKASLQ  
 WFNQALEDKSDAANSVETETPPITQPSFTFTLPAAPASPPTSLAPSTNPLLESLLKMQTPPSLPCCPE  
 SAGAATTEALSPPKTPSLLPPLGLSQSGPPGLLPSPSFDSPKPTTLGLIPAPSMVPATDTKAPPTLQAE  
 TATKPQATSAPSPAPKQSFLEGTQNTSPSSPAAPAAASSAPPMFKPIFTAPPKSEKEGPTPPGPSVTATAP  
 SSSSLPTTTSTTAPTQPVFSSMGPPASVPLPAPFFKQTTTPATAPTTTAPLFTGLASATSAVAPITSAS  
 PSTDSASKPAFGFNGSVSSSVSTTTSTATAASQPFLEFGAPQASAASTPAMGSIQFGKPPALPTTT  
 VTTFSSQLHTAVPTATSSSADFSGFGSTLATAPATSSQPTLTFSNTSTPTFNIPFGSSAKSPLPSYPG  
 ANPQPAFGAAEGQPPGAAPALAPSPGSSFTFGNSAAPAAAPTAPPPSMIKVVPAYVPTPIHPIFGGATH  
 SAFGLKATASAFGAPASSQPAFGGSTAVFFGAATSSGFGATTQTASSGSSSVFGSTTPSPFTFGGSAAP  
 AGSGSFSGINVTATPGSSSTTTGAFSFGAGQSGSTATSTPFAGGLGQNALGTTGQSTPFAPFNVSTTESKPVF  
 GGTATPTFGLNTPAPGVGTSGSSLSFGASSAPAQGFVGVAPFGSAALSFSIGAGSKTPGARQRLQARRQH  
 TRKK

>gi|4506181|ref|NP\_002778.1| proteasome alpha 2 subunit; proteasome  
 subunit HC3; proteasome component C3; macropain subunit C3;  
 multicatalytic endopeptidase complex subunit C3 [Homo sapiens]  
 MAERGYSFSLTTFSPSGKLVIQIYALAAVAGGAPSVGIIKAANGVVLATEKKQKSILYDERSVHKVEPITK  
 HIGLVYSGMGPDYRVLVHRARKLAQQYILVYQEPITPAQLVQRVASVMQEYTSQSGVRFPGVSLICGWN  
 EGRPYLFQSDPSGAYFAWKATAMGKNYVNGKTFLEKRYNEDLEDAIHTAILTLKESFEGQMTEDNIEV  
 GICNEAGFRRLTPTEVKDYLAIA

>gi|4506183|ref|NP\_002779.1| proteasome alpha 3 subunit isoform 1;  
 proteasome subunit C8; macropain subunit C8; multicatalytic  
 endopeptidase complex subunit C8 [Homo sapiens]  
 MSSIGTGYDLSASTFSPDGRVQVEYAMKAVENTSSTAIGIRCKDGVVFGVEKLVLSKLYEEGSKNRLFN  
 DRHVGMAVAGLLADARSLADIAREEASNFRSNFGYNIPLKHLADRVAMYVHAYTLYSAVRPFGCSFMLGS  
 YSVNDGAQLYIMIDPSGVSYGWCAIGKARQAATEIEKLQMKEMTCRDIVKEVAKIYIVHDEVKDKAF  
 ELELSWVGELTNGRHEIVPKDIRREAEKYAKESLKEEDESDDDNM

>gi|4506193|ref|NP\_002784.1| proteasome beta 1 subunit; proteasome  
 subunit HC5; proteasome component C5; macropain subunit C5; proteasome  
 gamma chain; multicatalytic endopeptidase complex subunit C5 [Homo  
 sapiens]  
 MLSSSTAMYSAPGRDLGMEPHRAAGPLQLRFSPYVFNNGGTILAIAGEDFAIVASDTRLSEGFSIHTRDSPK  
 CYKLTDKTVIGCSGFHGDCLTLTKIIEARLKMVKHSNNKAMTTGAIAAMLSTILYSRRFFPYVYNIIGG  
 LDEEGKGAUVSYFDPVGSYQRDSFKAGGSASAMLQPLLDNQVGFKNMQNVEHVPLSLDRAMRLVKDVFISA  
 AERDVYTGDLALRICIVTKEGIREETVSLRKD

>gi|20539647|ref|XP\_167259.1| similar to protease (prosome, macropain)  
 26S subunit, ATPase 1 [Rattus norvegicus] [Homo sapiens]  
 MSVVTLEEIIIDNHAIMSTSSILVDKDLLEPGCSVLLNHKVRVAVIWMDDTDLVTMMKVEKTPQETCV  
 DTGGGLDSQIQEIKEIILNIMKRWKYLHDGPKLIWELFLVAEEHAPSIMFIDEIDAIRTKRCDNSDSERE  
 IQQIMLEMLNQLDGFDSRGDVKVIISTRIETLDLALIRPGYTDRLKFLPDEKTKKHIFQMHTSSMTL  
 ANDAICTEASLMALKEHGMKVNTNENFKKSQENVLYKEQEDTPKGLCL

>gi|27479738|ref|XP\_210528.1| similar to protease (prosome, macropain)  
 26S subunit, ATPase 1 [Rattus norvegicus] [Homo sapiens]  
 MGESQSGGYGPGVCNKNGRTRKINMNLQLEWRRRKQRDQMLPANCHCHKVHAVIGVLMDDTDLPLFTVM  
 KVEKTPQETYADTGGEIKESVKPPLTQHEYYEETGVKPPPTGWGVILYGPPTVAEEHAPSTVFIDDINV  
 TGTKRYDSNSGGEIAIQRTMLELWNQLDGFDSRGDVKMHTSMTLADDVNLDDLIMTKDDLFGADIKAIK

EX03-029P

TEACLMALREPQNEENVLCCKQEGTPKGLYL

>gi|29727184|ref|XP\_292848.1| similar to protease (prosome, macropain)  
26S subunit, ATPase 1 [Rattus norvegicus] [Homo sapiens]  
MGQSQSGHGPSSGKKDDKDKKKKYEPSVPTVRVKKKKKTKGPDVASKLPLVTPHTQCRLKLLTLERIKD  
YLLMEEEFIRNQEQMKPLEEKQKEERSKVDDLRGTPIQSSGNWLLGPAQPGACRDGVLMDDDTDLPLVTV  
MKMEKTPQETYANIGGLDNQIQEIKEAVEFPLTHPEYYEEMGKPPKGVILYGGPGTGKTLSSKAVANQT  
SATFLRVVGSELIQKYLVAEEHELIMFTDEIGAIGTKRYDSNSGGRIDRKIKFSLPDERTKKRIFQNH  
SRMTLADSVTLDDLMVKKDDLSGADIKAICTEAGLMASRERRMKVTNEFFKKYKEMFFIRNRKAPLRGSI  
SSEPQLPSGKWLGDSSSTPEKDEQLVPKAGEDTPEGYLQQLMTQLFEQKEAKKFSRKSPELLEELASSLA

>gi|29736610|ref|XP\_293923.1| similar to protease (prosome, macropain)  
26S subunit, ATPase 1 [Homo sapiens]  
MIVEVEELPAVAAQVAKTRVAEKEEKTGQDVASKLPLVTLHTQCRLKLLKLERIKDYLLMVEEFIRNQ  
QIKLLEEKQEEGRSKVDDLRGTPMSVGNLEEIIDDNHAIIVSTSVGSEHYDSIISFVEKDLLEPGCSILLR  
HKVHAVIGVLMDDTGPLVTMMKVEKAPQETYVNTGGLDNQIQEIKESMELPLPHPEYYEEMGKPPKGV  
LCGPPGTATFLRVVGSELIQKYLGDGPKLVQVQVAEEHAPSIMFTDEIEAIGTKRYDSNSGGERIEQQ  
TMLELELLNQLGGFDSREDVKVIMATKQVETLDPVLIRPGRIDKIEFHLFDEKTKKHIFQIHTSRMTLA  
NDVTLDDLMKDDFSGADIKAICTEAGLMALREHRMKATNEDFKKSIESVLYKKHEGIPEGLYL

>gi|29740164|ref|XP\_294034.1| similar to protease (prosome, macropain)  
26S subunit, ATPase 1 [Rattus norvegicus] [Homo sapiens]  
MSVGTLEEINDSHAIVSTSVSGSHYANILSFVDKDLLATGCSVLLNHKVVHAMRGVLMDDVDPLVTVMKVE  
KVPQETYANTGRLDNQIQEIKESVELPLTHAEHYEEMGIKPPKGVILYGGPGIVKTLAKAVANQTSATF  
LKVVVGSELIQKYLGDGPKLVRELQVAGEHAPSIVFTDETDAIGTKRYDSNSGEAGLMALRERRMKATNE  
DFKKSKEENVLYKKQEGTPEGLSL

>gi|29737532|ref|XP\_294368.1| similar to protease (prosome, macropain)  
26S subunit, ATPase 1 [Homo sapiens]  
MVQSQSGHGPSSGKKDDKDKKKKYKPPVPTVRVGGKKKKTEGSAASKLPLVTPHTQCQLKLLKKQKQME  
PLEEKQEEERSKVDDLRGTPMSVGTLEEIINDSHATVSTSVGSERYVSILSFVDKDLLEPGCLVLLNHKV  
HAMIGVLMDDNMDPLVTVMKGLDNQSQEIKESVELPLTHPEYYEEMGIKPPKGVILYGGPGTEYALSIMFI  
DEIDAIGTKRYDSNSGSEIREIQRSALELLNQSDGFSRGGVVKVIMATNQIETLDPALIRPGCIDRKIEFP  
LHDENTKKRIFQIHTIRMTLANDVNLDDLVTRDDLSGADIKAICTEVGLMASRECRMQVKNEDFQKSKE  
NVLYKKQEGTPEGLYL

>gi|24430151|ref|NP\_002793.2| proteasome 26S ATPase subunit 1;  
proteasome 26S subunit, ATPase, 1; 26S protease regulatory subunit 4  
[Homo sapiens]  
MGQSQSGHGPSSGKKDDKDKKKKYEPVPTVRVGGKKKKTKGPDVASKLPLVTPHTQCRLKLLKLERIKD  
YLLMEEEFIRNQEQMKPLEEKQEEERSKVDDLRGTPMSVGTLEEIIDDNHAIIVSTSVGSEHYVSILSFVD  
KDLLEPGCSVLLNHKVVHAVIGVLMDDTDLPLVTVMKVEKAPQETYADIGGLDNQIQEIKESVELPLTHPEY  
YEEMGIKPPKGVILYGGPGTGKTLAKAVANQTSATFLRVVGSELIQKYLGDGPKLVRELFRVAEEHAPS  
IVFIDEIDAIGTKRYDSNSGGERIEIQRMTLELLNQLDGFSRGGVVKVIMATNRIETLDPALIRPGRIDRK  
IEFPLPDEKTKKRIFQIHTSRMTLADDVTLDDLMKDDLSGADIKAICTEAGLMALRERRMKVTNEDFK  
KSKENVLYKKQEGTPEGLYL

>gi|25777602|ref|NP\_002799.3| proteasome 26S non-ATPase subunit 2;  
tumor necrosis factor receptor-associated protein 2; TNFR-associated  
protein 2; 55.11 protein; 26S proteasome non-ATPase regulatory subunit  
2; 26S proteasome regulatory subunit S2; 26S proteasome subunit p97  
[Homo sapiens]  
MEEGGRDKAPVQPPQSPAAAPGGTDEKPSGKERRDAGDKDKEQELSEEDKQLQDELEMLVERLGEKDTSL  
YRPALEELRRQIRSSSTTSMTSPKPLKFLRPHYGLKEIYENMAPGENKRFAADIISVLAMTMSGERECL  
KYRLVGSQEELASWGHEYVRHLAGEVAKEWQELDDAEKVQREPLTLVKEIVPYNMAHNAEHEACDLME  
IEQVDMLEKDIDENAYAKVCLYLTSCVNYVPEPENSALLRCALGVFRKFSRFPALRLALMLNDMELVED  
IFTSCDKVVVQKQMAFMLGRHGVFLELSEDEVEEYEDLTEIMSNVQLNSNFLALARELDIMEPKVPDDIYK

EX03-029P

THLENNRFGSGSQVDSARMNLASSFVNGFVNAAFQDKLLTDDGNKWLYKNKDHGMLSAASISGMILLW  
DVDGGLTQIDKYLYSSEDIYKSGALLACGIVNSGVRNECDPALALLSDYVLHNSNTMRIGSIFGLGLAYA  
GSNREDVLTLLLPMVGDSKSSMEVAGVTALACGMIAGVSCNGDVTSTILQTIMEKSETELKDTYARWLPL  
GLGLNHLGKGEAIEAILAALEVSEPPFRSFANTLVDCAYAGSGNVLVQVQLLHICSEHFDSKEKEEDKD  
KKEKKDKKKEAPADMGAHQCVAVLGLIALIAMGEEIGAEMLRTFGHLLRYGEPTLRRAPPLALALISVS  
NPRNLNLDTLKFSHADPEVSYNSIFAMGMVSGTNNARLAAMLRLQAQYHAKDPNNLFMVRLAQGLTH  
LGKGTLLTLCFYHSDRQLMSQVAVAGLLTVLVSFLDVRNIIILGKSHYVLYGLVAAMQPRMLVTFDEELRPL  
PVSVRVGQAVDVVGAGKPKTITGFTHTTPVLLAHGERAEATEEFLPVTPILEGFVILRKNPNYDL

>gi|6382079|ref|NP\_006258.2| RAN binding protein 2; nucleoporin 358;  
nuclear pore complex protein Nup358; P270 [Homo sapiens]  
MRRSKADVERIYASVQGSTPSPRQKSMKGFYFAKLYEAEKEYDLAKKYICTYINVQERDPKAHRFLGLLY  
ELEENTDKAVECYRRSVELNPTQKDLVLKIAELLCKNDVTDGRAKYWLERAAKLPFGSPAIFYKLKEQLLD  
CEGEDGWNKFLDLIQSELYVRPDDVHVNIIRLVEVYRSTKRLKDAVAHCHEAERNIALRSSLEWNSCVVQT  
LKEYLESQCLESKSDWRATNTDLLAYANLMLLTSTRDVSQRELLQSFDLSALQSVKSLGGNDELISA  
TFLEMKGHFYMHAGSLLKMGQHSSNVQWRALSELALCYLIAFQVPRPKIKLIKGEAGQNLLEMMACDR  
LSQSGHMLNLSRGKQDFLKEIVETFANKSGQSALYDALFSSQSPKDTSLGSDDIGNIDVREPELDT  
RYDVGAIRAHNGSLQHLTWLGLQWNSLPALPGIRKWLKQLFHHLPHETSRLETNAPESICILDLEVLGL  
VVTSHLQLKEKCNHSHSSVQPLCLPLPVCKQLCTERQKSWWDVAVCTLIHRKAVPGNVAKLRLLVQHEIN  
TLRAQEKHGLQPALLVHWAECLOKGTGSLNSFYDQREYIGRSVHYWKKVPLLLKIIKKKNSIPEPIDPLF  
KHFSVDIQASEIVEYEEDAHITFAILDVANGNIEDAVTAFESIKSVSYWNALALIFHRKAEDIENDALS  
PEEQEACKNYLRKTRDYLIKIDDSNLSVVKLPVPLESVKEMLNSVMQLEDEYSEGGLPYKNKSLRN  
ADSEIKHSTPSPTKYSLSPSKSYKSPKTPPRAEDQNSLLKMICQQVEAIKKEMQELKLNSSNSASPHR  
WPTENYGPDSVPDGYQGSQTFHGAPLTVATTGPSVYYSQSPAYNSQYLLRPAANVTPTKGPVYGMNRLPP  
QQHIYAYPQQMHTPPVQSSSACMFSSQEMYGPPALRFESPATGILSPRGDDYFNYNVQQTSTNPLPEPGY  
VVTQPPPAAYSNSSELGLLLTSDKPLQGDGYSAGAKPIPGGQTIGPRNTFNFGSKNVSGISFTENMGSSQQ  
KNSGFRSSDDMTFFHGPQKSVFGTPTLETANKNHETDGGSAHGDDDDDPHFEPVPLPDKIEVKTGEED  
EEBFFCNRAKLFRRFVESKEWKEGIGNVKILRHKTSKIRLLMRREQVLKICANHYSISPMKLTNAGS  
DRSFVWALDYADELKPQELAIRFKTPEEAALFKCKFEEAQSILKAPGTNVAMASNQAVRIVKEPTSHD  
NKDICKSDAGNLNFEFQVAKKEGSSWHCNSCLKNASTAKKCVSCQNLNPSNKLGVPLAETVFTPKTS  
PENVDQRFALVTPKKKEGHWDCSICLVNNEPTVSRCIACQNTKSANKSGSSFVHQASFKFGQDLPKPKINS  
DFRSVSTKEGQWDCSACLQVNEGSSTKCAACQNPQRKQSLPATSIPTPASFKFGTSETSKTLKSGFEDMF  
AKKEGQWDCSSCLVRNEANATRCVACQNPDKPSPSTSVAPASFKFGTSETSKAPKSGFEGMFTKKEGQWDCSVCLVRNEA  
DCSVCLVRNEASATKCIACQNPQKQNTTSASVTPASSETSKAPKSGFEGMFTKKEGQWDCSVCLVRNEA  
SATKCIACQNPQKQNTTSASVTPASSETSKAPKSGFEGMFTKKEGQWDCSVCLVRNEASATKCIACQCP  
SKQNTTAISTPASSEISKAPKSGFEGMFTKKEGQWDCSVCCQVNESSSLKCVACDASKPTHKPIAEAPSA  
FTLGSEMKLHDSGSGVGTGFKSNFSEKASKFGNTEQGFKFGHVDQENSPSFMFQGSSTNTEFKSTKEGFS  
IPVSADGFKFGISEPGNQEKKEKPLENGTGFAQDISGQKNGRGVIFGQTSSTFTFADLAKSTSGEGFQ  
FGKDPNFKFGSGAGEKLFSSQYGMANKANTSGDFEKDDDAYKTEDSDDIHFEPVVMPEKVELVTGEE  
DEKVLYSQVRKLFRAEVSQWKEGRLNKLKNEVNGKRLMLMRREQVLKVCANHWITTTMNLKPLSG  
SDRAWMWLASDFSDGDAKLEQLAAKFKTPELAEEFKQKFEECQRLLLDIPLOTPHKLVDTGRAAKLIQRA  
EEMKSGLKDFKFTFLNDQTKVTEENKSGSGTGAAGASDTTIKPNPENTGPTLEWDNYDLREDALDDSVSS  
SSVHASPLASSPVRKNLFRFGESTTGPNFSFKSALSPSKSPAKLNQSGTSVGTDEESDVTQEEERDGYF  
EPVVPLPDLVEVSSGEENEQVVFSHRAKLYRYDKDVQWKEGIGDIKILQNYDNKQVRIVMRDQVLKL  
CANHRITPDMTLQNMKGTERVWLWACDFADGERKVEHLAVRFLQDVADSFKKIFDEAKTAQEKDSLIT  
PHVRSSTPRESPCGKIAVAVLEETTRETVDVIQGDVADATSEVVSSTSETTPKAVVSPPKFVFGSES  
VKSIFSSEKSKPFAFGNSSATGSLFGFSFNAPLKSNNSETSSVAQSGSESKEPKKCELSKNSDIEQSSD  
SKVKNLFAFPTEESSINYTFKTPKAKEKKKPEDSPSDDDLIVYELTPTAEQKALATKLLPPTFFCY  
KNRPDYVSEEEEDDEFETAVKKNLNGKLYLDGSEKCRPLEENTADNEKECIIVWEKKPTVEEKAKADTLK  
LPPTFFCGVCSDDTDEDNGNGEDFQSELOKVQEAQKSQTEIITSTDSVYTGTEVMVPSFCKSEEPDSIT  
KSISPSVSSETMDKPVLDLSTRKEIDTSTSQGESKIVSFGFGSSTGLSFADLASSNSGDFAFGSKDKNF  
QWANTGAAVFGTQSVGTQSAQVGEDEDEGSDEEVHNEIDHFEPIVSLPEVEVKSGEEDDEILFKERAKL  
YRWDRDVSQWKEGVDIKILWHTMKNYYRILMRDQVFKVCANHVITKTMLKPLNVSNNALVWTASDY  
ADGEAKVEQLAVRFTKEVADCFKTPTEECQQLNMLKQKHVSLAELSKETNPVVFPDVCADGELGRI  
TMELFSNIVPRTAENFRALCTGEKGFKNISIFHRVIPDFVCQGGDITKHDGTGGQSIYGDKFEDENFDV  
KHTGPGLLSMANQGQNTNNSQFVITLKAHLDPKHVVFVKGDMVTVKKIESFGSPKGSVCRRITITE

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